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CITATION:

HASEBE, SUKETSUGU. Studies on the Intrahepatic Nerves in Cirrhotic Liver. 日本外科宝函 1964, 33(2): 220-251

ISSUE DATE:

1964-03-01

URL:

http://hdl.handle.net/2433/205712

Studies on the Intrahepatic Nerves in Cirrhotic Liver

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Received for Publication Dec. 23, 1963

CONTENT

I. INTRODUCTION

There have been many investigations on the anatomy of the liver which is the largest parenchymal organ in the body having a complicated vascular structure and function and it is already well known that the innervation is achieved by the sympathetic, vagal and phrenic nerves and centripetal fibres running close to these. As the staining method made an improvement and advance, there appeared many reports of histological studies of the intrahepatic nerves made by RIEGELE[50], STOEHR[59)62)], KUBO[32)], KIMURA and SAI[29)], SUZUKI[55)56)] and others. These studies on the both intra- and extrahepatic innervation have been concerned exclusively around the liver hilum and it is widely conceived that the nerves of

the liver enter from the hilum to the intrahepatic space. Furthermore, not only there is no systematic study on the identification and course of the extrinsic fibres of the hepatic vein which is the only out-let system of the liver, but very few poor reports have been published on the intrahepatic fibres which enter the liver by way of the hepatic vein, while there are many on the fibres from the liver hilum.

There are also many studies on morphological changes in the intrahepatic blood vessels of liver cirrhosis and ascitic dogs whose liver resembles cirrhosis.

It was pointed out by Child and others that the hilar occlusion of the artery draining into the liver does not result in liver necrosis in cases of liver cirrhosis having an accumulation of ascitic fluid. Although there is no theory widely accepted concerning the mechanism of development of liver necrosis caused by the ligation of the hepatic artery, HONJO[22)23)24)] insisted that hypoxic condition due to liver congestion caused by portal circulatory disturbance following hepatic artery ligation must be the very reason of the liver necrosis. YOSHITOMI[66)] in our clinic demonstrated in normal dogs using polyester resin cast preparation that marked contraction of the sphincter in the hepatic venules can be observed following the ligation of the hepatic artery, which leads to portal congestion. MORITA[45)], also in our clinic, reported that such contraction of the sphincter is hardly observed following hepatic artery ligation in ascitic dogs, and portal congestion hardly occurs consequently without liver necrosis.

In 1954, Child attempted pharmacological experiment in cirrhotic liver, and observed that portal pressure arises following epinephrine administration in normal human liver, while the pressure rather falls in cirrhotic patients. In liver cirrhosis and ascitic dogs with the liver resembling cirrhosis in which characteristic and functional changes of intrahepatic circulation develop, attitude of the nervous tissue distributed to intrahepatic blood vessels has been left in obscurity, except FUKUOKA's[14)] report that degeneration of the nervous fibre could not be observed in progressive liver cirrhosis in albino rats.

As a part of the studies on liver cirrhosis in our clinic, the author of the present experiment carried out histological studies of the nervous tissue in the liver of normal and experimentally produced ascitic dogs, which have the liver resembling cirrhosis, and changes in portal pressure after administration of epinephrine was also studied and, at the same time, histological study was carried out in human cirrhotic liver and some informations were obtained.

II. HISTOLOGICAL STUDIES ON THE INTRAHEPATIC NERVES

1. Materials and methods

In normal and ascitic dogs, the abdomen was opened under intravenous anesthesia of isozol. Cannulas were inserted into the portal vein and hepatic artery and the liver was perfused with 10% neutral formalin solution. Immediately after fixation of the liver with formalin within the body, the liver was totally extirpated. In clinical cases, the livers were extirpated at autopsy of cirrhotic patients in a condition as fresh as possible. Both of the extirpated livers were immersed in 10% neutral formalin solution for more than 2 months.

Sections were taken from hilar area, opening area of the hepatic vein to the inferior vena cava, peripheral marginal portions and so on. Slices of 20 to 30μ in thickness were made from these sections and fixed again in 10% neutral formalin solution for more than

a week.

For axon staining, Suzuki's modified method of Bielschowsky's staining was employed with additional preparative treatment with 80 to 90% ethanol and for myelin sheath staining Sugamo's method was employed.

2. Liver of normal dogs

i. Materials

Six adult mongrel dogs of both sexes weighing 10 to 16kg were used.

ii. Hilar area and peripheral area

Bundles of unmyelinated nerve fibres of various sizes enter the liver hilum running along the hepatic artery, portal vein and bile duct. Some of these bundles of unmyelinated fibres are accompanied by myelinated fibres, although the latter is found more scarcely than the former. Most of the myelinated fibres which enter from the hilum form several bundles (Fig. 1), some of which were consisted of many bundle of ten or so (Fig. 2). Most of myelinated fibres had reasonable size, and among those which run along the hepatic artery extremely large bundles were sometimes observed (Fig. 3 and 4).

These bundles of nervous fibres which enter from the liver hilum spread to the peripheral area running along the blood vessels on the way of which branching in a shape of fork (Fig. 5) or tree, communicating to each other to form plexus (Fig. 6 and 7), on the wall of the vessels. Running along the blood vessels, the bundles provide branches to the branches of the vessels, decreasing their size gradually (Fig. 8). At the small peripheral vessels, number of fibres markedly decreases and comes to a few or single ones. The fibres further branch and enter the lobules (Fig. 9) and finally run interspace of the hepatic cell cords (Fig. 10). Both myelinated and unmyelinated fibres of the nerve which enter from the liver hilum are abundantly found in the hilar area,which decrease markedly in number as it spread to the periphery. Distribution of the nerve is abundant in the hepatic artery compared with other vessels.

iii. Nerves of hepatic vein

Bundles of unmyelinated fibres accompanied by a few myelinated fibres enter the hepatic vein from the opening site of the hepatic vein to the inferior vena cava (Fig. 11), and distribute themselves to the adventitia (Fig. 12). These bundles of the nervous fibres run in longitudinal and oblique direction in the adventitia, forming plexus with communications to each other. Most of unmyelinated fibres of the hepatic vein are small in size (Fig. 13), some of them being exceptionally large. Both myelinated and unmyelinated fibres of the nerves of the hepatic vein are mostly distributed in the opening site of the hepatic vein to the inferior vena cava. The number of fibres markedly decrease as the vessels branch and become small (Fig. 14). Myelinated fibres of the hepatic vein are found here and there in the adventitia, frequently running alone (Fig. 18), although sometimes forming a bundle of a few stripes (Fig. 15, 16 and 17). Number of the myelinated fibres of the hepatic vein at the opening site to the inferior vena cava increases in the proportion of the size of the vessels, showing the same individual differences as in hilar area. Most of these myelinated fibres had moderate size and some of these had small one. However, fibres of a large size were not found as in the liver hilum. Number of myelinated and unmyelinated fibres in the hepatic vein is found to be less compared with those of the hepatic artery and portal vein, from the aspect of size of the vessels. Large

size fibres are found running in the adventitia, which were regarded as centripetal fibres from silver impregnating method. Some of these bifurcate in the shape of fork, or give small branches on the way, forming a loop in parts (Fig. 19 and 20). Moreover, some of these form a spiral shape (Fig. 21), or form free sensory ending by the nervous syncytium (Fig. 22). The hepatic vein sometimes runs close to the Glisson's sheath. However, communication of nervous fibres between Glisson's sheath and the hepatic vein was not observed. Fairly abundant distribution of nervous fibres was observed around the sphincter of the hepatic vein. However, neither finding of entering the sphincter of nervous element nor nervous ending in the muscle cells was observed (Fig. 23, 24 and 25).

iv. Summary

From these findings the nerves of the liver can be roughly divided into two groups, one entering from the liver hilum and another from opening site of the hepatic vein to the inferior vena cava, the former distributing along the hepatic artery, portal vein and bile duct and the latter chiefly distributing to the hepatic vein. It was clarified that the nerves of the hepatic vein is similarly consisted of autonomic and sensory nerves as the nerves of other intrahepatic vessel systems.

3. Liver of ascitic dogs

i. Production of ascitic dogs

Method of McKee was followed for production of ascitic dogs. Thoracic cavity was opened in the right 6th intercostal space on the mammillary line under intravenous injection of isozol of 20mg/kg body weight and intratracheal anesthesia, and the inferior vena cava was reached. The inferior vena cava was isolated from the phrenic nerve and surrounding tissues and constricted with a cellophane tape of 1cm in width.

ii. Materials

Thirty-six ascitic dogs were used 7 to 140 days after the constriction of the inferior vena cava.

iii. Histological findings of nerves

In ascitic dogs of 27th postoperative day, there appeared irregular swelling and granular degeneration in the myelinated nervous fibres of the hepatic vein (Fig. 26, 27 and 28) and swelling of Schwann's cells of small bundles in the adventitia of the hepatic vein (Fig. 29 and 30). In ascitic dogs of 36th postoperative day, irregular swelling of myelin sheath, vacuole formation (Fig. 32), drop-shaped fragmentation (Fig. 33 and 34) and irregular course of axon (Fig. 35) were observed in the portal vein besides degeneration of the nerves of the hepatic vein (Fig. 31). In ascitic dogs of 60th postoperative day, there appeared vacuole formation in the nucleus of swollen Schwann's cell of the nervous fibres which run in the wall of the hepatic vein (Fig. 36 and 37), furthermore, in the hepatic vein of moderate size severance and fragmentation of the axon were observed (Fig. 38 and 39). Fragmentation and granular degeneration were also observed in the axon of extremely fine bundle of the peripheral portal branches (Fig. 40 and 41). In ascitic dogs of 100th postoperative day, nodular swelling and chaplet-like degeneration were found in most of myelinated fibres of the hepatic vein (Fig. 42, 43, 44 and 45). In ascitic dogs of 130th postoperative day, besides fibres of the portal and hepatic vein, drop-shaped degeneration was observed in the myelinated fibers of the hepatic artery (Fig. 46, 47 and 48). In the peripheral arterial branches also tortuosity and fragmentation of the axon were observed

(Fig. 49 and 50).

iv. Summary

Findings of degeneration appeared in ascitic dogs about a month after the operation in the nerves which distribute to the hepatic and portal veins, and the degree of the degeneration advanced in the proportion of postoperative days. Degenerative change in the nerves of the portal and hepatic veins in ascitic dogs more advanced 100 days after the operation compared with that before this date, the degree of which being more pronounced in the nerves of the hepatic vein. Degenerative change appeared in the nerves of the hepatic artery in ascitic dogs 130 days after the operation. Whereas degeneration of myelinated fibres was observed in large vessels of the portal and hepatic veins and hepatic artery, degeneration of unmyelinated fibres had a tendency to occur more frequently in the peripheral small vessels.

4. Cirrhotic liver in man

i. Materials

Livers of Laennec's cirrhosis and fatty cirrhosis at autopsy were used in as fresh a condition as possible.

ii. Histological findings of nerves

At the liver hilum, bundles of unmyelinated nervous fibres of various sizes enter the liver along the vessels, some of which contained considerably many myelinated fibers. Most of myelinated fibres showed irregular and granular swelling and fragmentation at the hilum (Fig. 52, 53 and 54), and irregular course and severance were also observed (Fig. 56, 57 and 58). Similar degeneration was observed in myelinated and unmyelinated fibres in the nerves distributing to the hepatic vein from its opening site to the inferior vena cava as in the hilum (Fig. 59, 60 and 61).

iii. Summary

In the liver of man also, 2 groups of the nerves were ebserved to enter the liver from the hilum and opening site of the hepatic vein to the inferior vena cava. Nervous fibers of each group are extremely abundant compared with those in dogs.

In cirrhotic livers of man, degeneration of fibers with and without myelin sheath in the nerves distributing to the hilar area and hepatic vein was observed, the degree of which being more pronounced than in ascitic dogs.

III. FLUCTUATION OF PORTAL PRESSURE AT EPINEPHRINE ADMINISTRATION

1. Materials

Six ascitic dogs of respectively 1 week, 2 weeks, 4 weeks, 5 weeks, 6 weeks and 2 months after the constriction of the thoracic inferior vena cava were subjected to the experiment. As control animals 11 adult healthy mongrel dogs weighing 8 to 14kg were used.

2. Methods

Experimental dog was fixed on the back. The abdomen was opened under intravenous anesthesia of isozol of 20mg/kg body weight. A small incision was laid in a branch of the splenic vein and a polyethylene tube of about 1 mm in diameter was inserted. Top of the tube was fixed in the portal trunk and portal pressure was measured with heparinized saline solution. Epinephrine used here was " Adrenaline Chloride-Sankyo". Epine-

phrine of 10 γ and 50 γ was regarded as small dosis and large dosis, respectively, and infused into the branch of the superior mesenteric vein. The pressure measurement was performed with the lapse of time.

3. Result

i. In normal dogs

Although there was individual difference in fluctuation of portal pressure, elevation of the pressure was observed immediately after infusion of both 10 γ and 50 γ of epinephrine. In the infusion of 10γ, portal pressure reached its maximum elevation of 30mmH_2O 1 minute after infusion, which restored to the previous level 7 minutes after infusion. When 50γ of epinephrine was infused, the pressure elevated to its peak by 54 mmH_2O 1 minute and 10 seconds after infusion, which was followed by a tendency to restore to the previous level 10 minutes after infusion.

ii. In ascitic dogs

Fluctuation of portal pressure in ascitic dogs 1 week after the operation showed little significant difference after infusion of epinephrine of both 10 γ and 50 γ compared with that of normal dogs.

In ascitic dogs 3 weeks after the operation, portal pressure showed the maximum elevation of 56 mmH_2O 1 minute and 20 seconds after infusion of epinephrine of 10γ and when 50γ of epinephrine was infused the pressure reached its peak by 94 mmH_2O elevation 2 minutes after infusion. In ascitic dogs 4 weeks after the operation, interval of time between infusion and pressure elevation was prolonged, that is, at 10 γ infusion the pressure showed the maximum elevation of 85 mmH_2O 3 minutes and 20 seconds after infusion, and at 50γ infusion maximum elevation was as prominent as 144 mmH_2O 3 minutes and 40 seconds after infusion and the pressure restoration was also delayed.

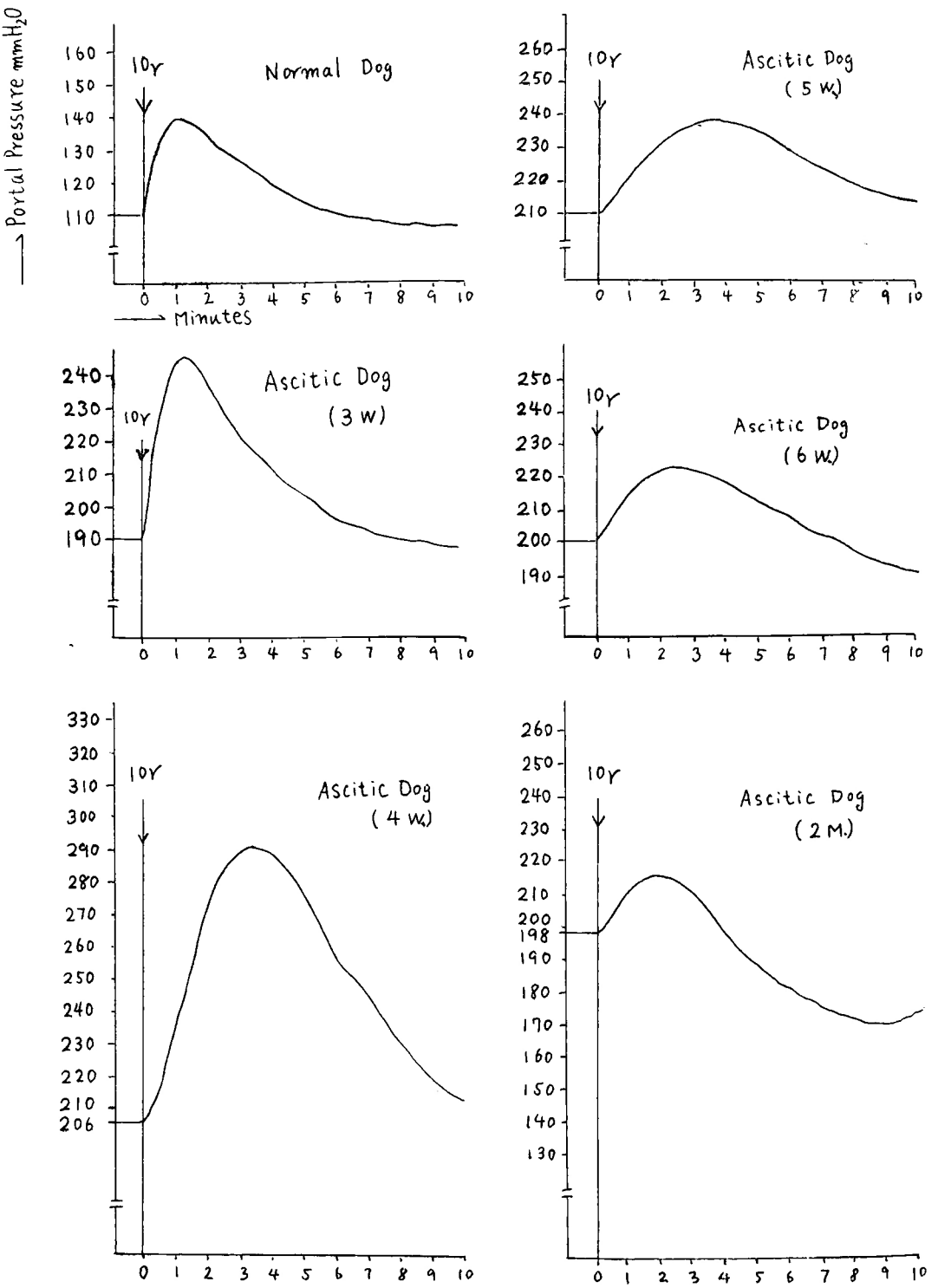
In ascitic dogs 5 weeks after the operation, portal pressure showed the maximum elevation of 29 mmH_2O 3 minutes and 30 seconds after 10 γ infusion and 48 mmH_2O 3 minutes and 50 seconds after 50 γ infusion, revealing a prolongation of time interval to pressure elevation with a tendency of decrease in the elevation.

In ascitic dogs 6 weeks after the operation, time interval to the pressure elevation was shortened slightly showing its maximum elevation of 22 mmH_2O 2 minutes and 20 seconds after 10 γ infusion and 44 mmH_2O 2 minutes and 50 seconds after 50 γ infusion. The range of the pressure elevation decreased in these animals and after portal pressure restored to the previous level, it showed continuous fall thereafter.

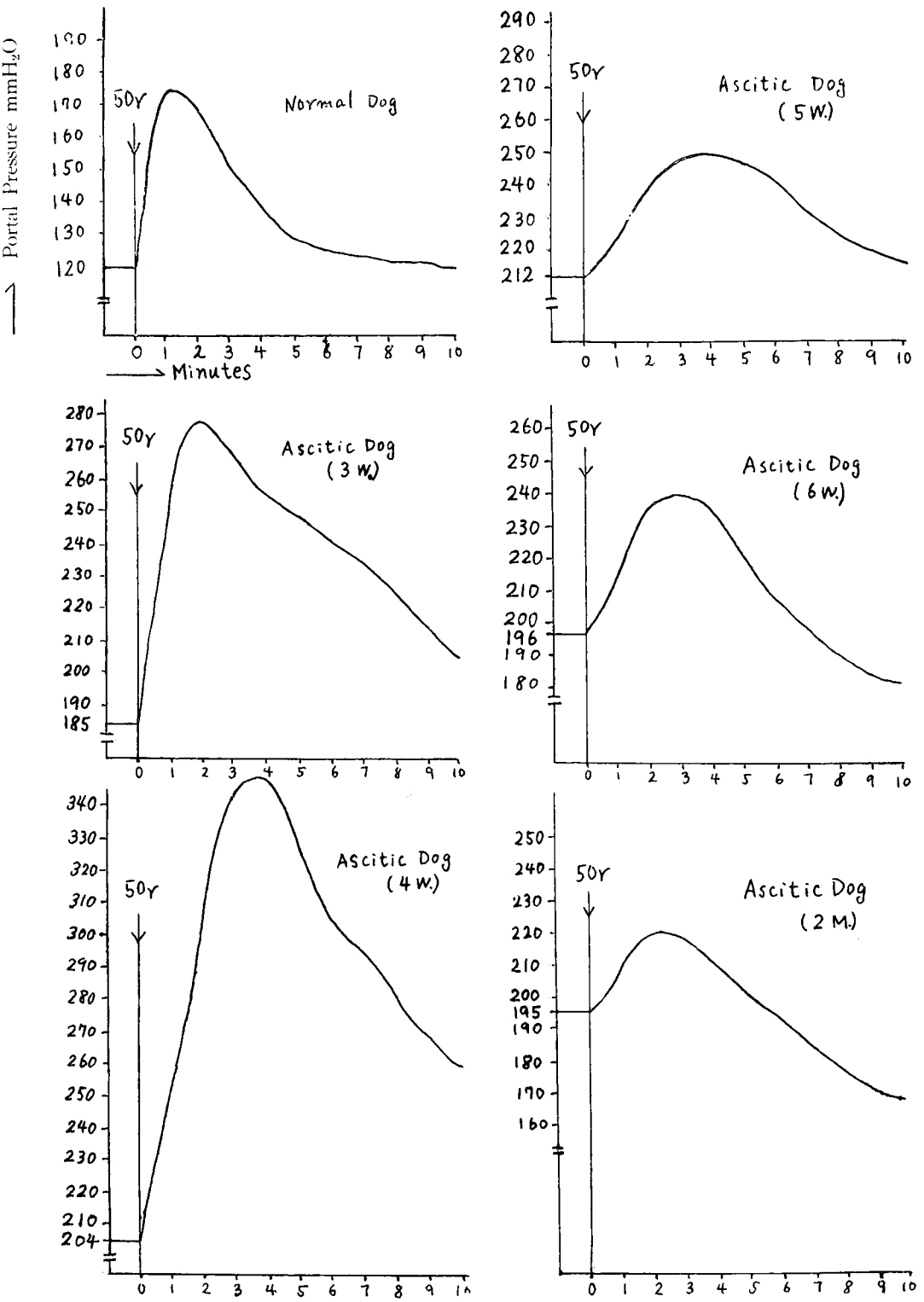
In ascitic dogs 2 months after the operation, although time interval to the maximum elevation was prolonged compared with that in normal dogs, it was slightly shortened being 1 minute and 40 seconds and 2 minutes and 20 seconds after 10γ and 50γ infusion, respectively, elevation of portal pressure also being markedly decreased to be 18 mmH_2O and 26 mmH_2O, respectively. Portal pressure rapidly restored to the previous level, showing further fall of 27 mmH_2O and 35 mmH_2O, respectively, range of which surpassed that of the elevation (Tab. 1 and 2).

iii. Summary

At the measurement of portal pressure after epinephrine infusion of 10γ and 50γ into a branch of the superior mesenteric vein, the pressure arose immediately after infusion in normal dogs, which was followed by gradual restoration to the previous level. Until a



Tab. 1. Fluctuation of portal pressure after administration of 10γ epinephrine from the superior mesenteric vein.



Tab. 2. Fluctuation of portal pressure after administration of 50γ epinephrine from the superior mesenteric vein

month after the operation, however, in ascitic dogs, time interval to the maximum portal pressure elevation was prolonged and the elevation was pronounced depending upon the postoperative interval of time. In ascitic dogs of more than a month after the operation, the range of elevation was rather decreased and the pressure rapidly restored to the previous level, which was further followed by marked fall exceeding the range of the elevation.

IV. DISCUSSION

Anatomical studies on the hepatic nerves have been carried out around the hilar area. According to the reports hitherto been published, it has been said that the sympathetic nerve enters the liver in two anterior and posterior groups through the right and left major splanchnic nerve, coeliac and hepatic plexus, one running along the hepatic artery, another along the portal vein. Concerning the vagus, the hepatic branch originating from the anterior stem of the esophageal plexus which is consisted of the left vagal nerve enters the liver communicating with the fibers from the coeliac plexus to form the hepatic plexus. There are reports of MITCHELL[42], LEWIS[34], POPPER and SCHAFFNER[49] and SUZUKI[55] on the distribution of the phrenic nerve to the liver. According to SUZUKI, the phrenic nerve forms a small phrenic ganglion below the diaphragm and the branches from this enter the liver by way of supporting tissues of the organ.

HONDA[19] studied on the extrinsic fibers with myelin sheath in innervation of the liver in dogs, and observed that most of them are consisted of centripetal fibres of the posterior route originating from posterior ganglion and fibers of the anterior route and centrifugal fibers of the posterior route are very few. Also he observed that the vagal nerve distributes to the liver as the fibers with myelin sheath. The intrahepatic nerve has been investigated since early days by PFLÜGER[48], BERKLEY[4], KOROLKOW[31], NESTEROWSKY[47] and others. Most of these were concerned with indirect elements from the aspect of staining method. With the technical advance of silver impregnating method, however, there appeared studies of IHARA[26], RIEGELE[50] and STOEHR[59], which gradually corrected the misunderstandings hitherto been done.

Despite these studies, opinions did not come to an accordance concerning the intrahepatic existence of myelinated fibres and ganglion cells. KUBO[32] later ascertained the intrahepatic existence of the myelinated fibres and ganglion cells and asserted that the nerves entering the liver are essentially consisted of numerous unmyelinated fibres and extremely few fibres with myelin sheath. Concerning the intrahepatic sensory nerve, SETO[54] insisted that there exists no sensory ending within the liver. On the other hand, MITCHELL[42] demonstrated the photographs of the myelinated fibres within the lobules of the liver, and KIMURA and SAI[29] ascertained the report of MITCHELL and demonstrated by severance experiment that these fibers are centripetal belonging to the spinal segments of Th_3 to L_2. They further discovered Pacini's corpuscle and sensory ending apparatus which deserve to be called SAI's corpuscle within Glisson's sheath of the left lobe of human liver. SUZUKI[55][56] reported that small number of myelinated fibres and far more small number of ganglion cells are found in the hilar area and he divided interstitial cells from Kupffer's cells within the lobules. He asserted that the nervous fibers which run in the hepatic parenchyma are unmyelinated, having two types of conjugation of nervous ending to hepatic cells in the lobules.

Concerning the nerves of the hepatic vein, RIEGELE[50] observed a few and considerably fine unmyelinated fibers in the wall of the hepatic and its sublobular veins. KUBO[32] reported that a few small fibres are found in various directions, although the central vein is distributed by very few nervous fibres. SAI[65] observed the sensory nerves in both interlobular arteries and veins, as well as in the central vein. SUZUKI[56] asserted that the nerve which enters the liver from the hilum with the portal vein forms a plexus of unmyelinated fibers containing Schwann's cells in the interlobular connective tissue. A singular unmyelinated bundle originating from this plexus runs in the direction of the central vein passing through interspace between the wall of sinusoids and hepatic cells, giving branches on its course. All these reports are of opinion that these nervous fibers enter from the hilum.

As has been surveyed, studies on the hepatic nerves have been concerned with the hilar area no matter which extra- or intrahepatic nerves, and it has been accepted that the hepatic nerves enter the liver exclusively from the hilum.

As to the intrahepatic nerves, presence or absence of fibers with myelin sheath, ganglion cells and sensory endings has been discussed. Whereas there have been deliberate studies on the nerves of the in-let vessel system and bile duct, no study was concerned with systematic research on the innervation of the hepatic vein, which is the out-let vessel of the liver, and what is more, there is no decisive report on the site of entering of the nerve to the hepatic vein and existence of the fibers with myelin sheath in the liver.

The author of the present paper carried out studies on the nerve of the hepatic vein and ascertained the existence of the nerve which chiefly distributes itself to the hepatic vein system entering the liver from the opening site of the hepatic vein to the inferior vena cava, besides those entering from the hilum together with the hepatic artery, portal vein and bile duct. Furthermore, it was also ascertained that these nerves of the hepatic vein are consisted of the autonomic and sensory nerves, and abundantly distributed particularly in the adventitia of the hepatic vein near its opening site to the inferior vena cava. Although the extrahepatic pathway of the nerves of the hepatic vein was not studied, in the present experiment, some interesting informations on the hepatic innervation will be brought about by these findings.

Concerning the problem of conjugation between nervous element and individual cells, discussions are being done on the relationship between smooth muscle cells and the nervous system. NAKAMURA[46] studied deliberately on the innervation of submandibular and sublingual gland, and reported that it was impossible to obtain a finding of the nervous element entering the cells. CHENG[7] also reported, according to the results of his studies in the carotid artery, abdominal aorta and inferior vena cava in dogs and the popliteal vein in man, that most of centripetal nervous fibres end in the connective tissue with free ending, without findings of contact with or entering the muscle cells, and although many "syncytium nerveux" of Jabonero were observed in the adventitia, net-work of the autonomic nervous ending was not observed in the media and intima. In the present experiment also, no nervous element was observed to be entering or distributing to the sphincter, though the nervous fibers were found around the sphincter of the hepatic vein.

Concerning the morphological changes in the intrahepatic vascular system of cirrhotic liver, HERRICK[18] pointed out an appearance of abnormal shunt between intrahepatic artery and intrahepatic portal system and sought the mechanism of portal hypertension in the pos-

sibility that the influence of hepatic arterial pressure would be readily reflected on portal pressure and further presumed that the fibrosis would enhance sclerotic change of the vessel wall causing decrease in diametral change of the vessels. McINDOE[37] pointed out decrease in total vascular bed and MADDEN[36] decrease in hepatic venous vascular bed in cirrhotic liver. MORITA[45], in our clinic, observed in a month aged ascitic dogs produced by constriction of the thoracic inferior vena cava, fibrosing process in the central area and formation of small lumens lined with endothelium presumably originating from sinusoid and reported that ligation of the hepatic artery in these animals did not result in macro- and microscopic liver congestion as was observed in normal dogs.

Response of the nervous tissue distributing to the intrahepatic vascular system in cirrhotic liver and liver of ascitic dogs resembling cirrhotic ones has been left in obscurity. There is the only report of FUKUOKA[14] that the nervous fibres were more abundantly observed in progressive cirrhosis of albino rats compared with those in normal liver, but degeneration was not observed.

The author of the present paper observed a finding of obvious degeneration of the intrahepatic nerves in the liver of ascitic dogs resembling cirrhosis and human cirrhotic liver. In the nerves of intrahepatic vascular system in ascitic dogs, degeneration was observed as postoperative days had passed, and degeneration was more pronounced in human cirrhotic liver than in ascitic dogs.

It is considered that besides cell infiltration, exudation and tissue edema have an important significance in the change of nervous element at the time of acute or chronic inflammation. For instance, it is widely known that mycobacterium leprae intensely invades the peripheral nerves and diphthery toxin generally degenerates nervous element regardless of infiltration of inflammatory cells. ARAKI[1] observed ruined findings of the vascular nerves in the site of gastric ulcer and he conceived dysfunction of the autonomic nerve as one of the etiologic factors of gastric ulcer. It is an important problem whether the nervous tissue in neoplasms is newly growing one in parallel with tumor growth or destructive product of disappearing one. KIMURA[28] insisted that principal factor of the nervous destruction in cancer is nutritional disturbance of the nerve caused by compression and it is generally hard to observe findings of chemical irritation as in inflammations. HAKODA[17] is of opinion that degeneration of the nerves in the liver caused by growth of YOSHIDA sarcoma is due to nerve toxin.

As is understood from the above, various factors can be considered in the mechanism of nervous degeneration. The author attempted following consideration concerning the factors of nervous degeneration in cirrhotic liver.

STOEHR[63] asserted that it is impossible for even a single blood cell to pass through the capillary without cooperation of the autonomic nerve. ARAKI[1] maintained that regardless of character of the causes all the degeneration and necrosis of tissue is enhanced by the change of vascular wall which premises some modulation of the vascular nerve. FUKUI[12][13] described that in existence of degeneration of the vascular nerve, capillary wall controlled by this nerve also necessarily encounters some change, with resulting emigration of blood component, which aggravates damage of the vascular nerve and thus forming vicious cycle, process of destruction advances. RÖSSLE[52] interpreted cirrhotic change in liver cirrhosis as a serous inflammatory process associated with increased permeability of the

capillary. The fact that degeneration of the nerve appears in the portal and hepatic vein towards a month after the constriction in ascitic dogs, at which time central congestion becomes marked and fibrosis appears, suggests that this degeneration is the result of efforts to adjust abnormal intrahepatic hemodynamics due to congestion and fibrosis and exudation of blood component caused by increased permeability of the capillary. In cirrhotic liver and that in ascitic dogs resembling cirrhosis in which abnormal circulation, necrosis of parenchyma cells and hyperplasia of connective tissue are observed, it cannot be neglected that intrahepatic vascular system largely participates in this cirrhotic process and vascular neurogenic factor should be emphasized in the development of the process.

If one considers possible entrance of the nervous fibers to the liver by way of the thoracic inferior vena cava, it may well be presumed that degeneration of intrahepatic nerves observed in ascitic dogs is associated with damage to the nervous element brought about by the constricting procedure of the thoracic inferior vena cava at production of ascitic dogs. Degeneration of the intrahepatic nerves in ascitic dogs, however, is observed not only in the hepatic vein but in the hepatic artery and portal vein and the degeneration is markedly observed also in human cirrhotic liver. From these findings, it might be justifiably conceived that degeneration of intrahepatic nerves in ascitic dogs is not caused by the procedure itself of constricting the inferior vena cava.

Studies carried out up to present on the function of the splanchnic nerve to the liver have obtained approximately similar results. BAYLISS and STARLING[3] observed contraction of the portal vein caused by stimulation on the splanchnic nerve. BURTON-OPITZ[6], BAUER[2] and WAKIM[67] reported that stimulation on the hepatic plexus resulted in contraction of the hepatic artery and portal vein.

Pharmacological studies on neurogenic adjustment of intrahepatic circulation using epinephrine has been carried out since early days as well as physiological studies. SCHMIDT[57] demonstrated that utmost decrease in portal flow is observed in the moment of maximum portal hypertension caused by epinephrine. BURTON-OPITZ[5][6] reported that epinephrine has an effect to contract intrahepatic arterial and portal branches.

MACLEOD and PEARCE[35] and MACLAUGHRINE[40] also observed contracting effect of epinephrine on intrahepatic portal branches. Furthermore, EDMUNDS[11], CLARK[9], GRIFFITH and EMERY[16] and others demonstrated that contraction of intrahepatic portal and arterial branches is brought about by stimulation on the branches of the sympathicus or epinephrine injection of certain dosis. MCMICHAEL[41] presumed that contracting effect of epinephrine does not act on the sublobular hepatic vein, but on the intrahepatic portal system.

As is described in the above, it is widely approved of by many researchers that stimulation on the splanchnic nerve and administration of epinephrine cause the contraction of the intrahepatic portal system, with resulting portal hypertension. However, there is an impression that physiological and pharmacological studies on intrahepatic circulation in cirrhotic liver are scarcely seen compared with morphological one.

CHILD[8] observed that epinephrine administration (0.5 ml 1 : 1000) from the superior mesenteric vein resulted in portal hypertension in patients having normal liver and normal portal pressure and also in those having moderate liver failure and slight portal hypertension, whereas, on the contrary, administration of epinephrine of similar dosis resulted in immediate fall of portal pressure in patients having progressive cirrhotic liver and serious

portal hypertension. He interpreted such a strange response of portal pressure as follows; 1) contractability is remarkably restrained and the vessels are deprived of the ability to respond to corresponding stimulation in cirrhotic liver, owing to its cirrhotic structure, 2) as the intrahepatic vascular system have encountered marked change during cirrhotic process, it must be in a state to have lost its ability to respond to epinephrine, 3) there exists some abnormal shunt between each of the hepatic artery, portal and hepatic veins, which might be presumably able to reverse regular response to epinephrine completely. Child, however, pointed out himself that so much is needed to demonstrate his interpretation.

In the present experiment, it was observed, at infusion of 10γ and 50γ of epinephrine from the superior mesenteric vein, that portal pressure in ascitic dogs until 1 month after the operation arose as postoperative day passed markedly exceeding the degree of elevation in normal dogs, whereas in ascitic dogs aged more than a month after the operation, elevation of portal pressure markedly decreased being followed by rapid restoration to the previous level and further fall also markedly exceeding the degree of the elevation. This finding is interpreted to suggest that contractive response of the intrahepatic portal system to epinephrine in ascitic dogs is temporarily accentuated after the operation, which is however, gradually weakened in one-way path. Close relationship of this finding to morphological change of the intrahepatic nerves of the portal vein is also suggested from the observation on the process of degeneration of the intrahepatic nerves associated with the contractive response. From these observations, it is assumed that in the change of portal pressure in pathologic liver, hypofunction of the vascular nerve is an important factor, besides possible participation of various factors insisted by Child and others. It is assumed that marked degeneration of the nerves observed in human cirrhotic liver also strongly suggests participation of neurogenic factor in change of portal pressure in pathologic liver.

Concerning the hepatic vein as the out-let system of the liver, MAUTNER and PICK[38] established the concept of so-called "Speerer Mechanismus", and BAUER and DALE[2] accentuated the significance of powerful bundle of smooth muscle at the opening site of the hepatic vein to the inferior vena cava and demonstrated constant increase in liver out-flow caused by epinephrine. They accepted this finding to reveal that this hormone acts in dogs to relax the sphincter mechanism scattered around the opening site of the hepatic vein to the inferior vena cava, with resulting large amount of liver out-flow to the inferior vena cava.

DEYSACH[10] observed that "small sluice channel" postulated by himself comes to open by epinephrine. KNISELY[30] asserted that out-let sphincter as well as DEYSACH's "sluice channel" plays an important role in the mechanism of blood reserve within the liver, and once contracted sphincter is never opened by blood pressure of any degree. MORENO and LOUIS[43] observed when contrast medium was injected into liver parenchyma, powerful sphincter around the opening site of the hepatic vein to the inferior vena cava contracted tightly and intermediate portion of the hepatic vein was dilated gradually to extraordinary size and they reported that such dilatation of the hepatic vein was well inhibited by administration of epinephrine prior to the injection of contrast medium into liver parenchyma. LAMSON and ROCCA[33] thought the liver to be an organ which posesses a constrictor mechanism at venous side of the capillary and reported that the constrictor mechanism has neurogenic control. ROSENBLUTH[51] and SNYDER[58] reported that the sphincter is spiral

smooth muscle surrounding vessel wall, which receives distribution of the autonomic nerve cooperating with DEYSACH's channel. THOMAS and ESSEX[64] observed in their experiment of polyethylene infusion that the smaller the venous branches were, the stronger the contraction, and utmost contraction of the sphincter of the hepatic vein was observed 2 hours after interruption of the hepatic artery. YOSHITOMI[66], in our clinic, observed in resin cast preparations contraction of the hepatic venous sphincter immediately after interruption of the hepatic artery for a few hours, and he conceived that this contraction is the important factor of the congestion which develops immediately after the interruption. MORITA[45], also in our clinic, observed in his histological studies the identical finding to the result of YOSHITOMI and thought that inadequate contraction of the hepatic venous sphincter in ascitic dogs plays, as well as formation of intrahepatic shunt, the important role in lessening the congestion of portal blood after the interruption. As mentioned in the above, it was clarified in the present experiment that the hepatic vein, which has characteristic architecture and function in intrahepatic vascular system, is controlled by the autonomic and sensory nerves besides those from the hepatic hilum, which is interpreted to have close association to various characteristics of the hepatic vein.

HONJIN[20][21] strongly suggested that the system of vegetative nerve is constituted of two different components of neuron and a large net-work of nervous ending called neural terminal net, and concluded that neural impulse is not conducted immediately to the referred cells, but through neural terminal net, which belongs neither to the sympathicus nor parasympathicus. NAKAMURA[46] positively supported Honjin's *two component theory* of the autonomic nerve and thought that the neural terminal net shows various response depending on the difference of impulses from the extrinsic fibres, which controls the neural terminal net, and metabolic function of the referred cells is regulated through the response. Distribution of the sympathicus and sensory nerve to the hepatic vein is interpreted that the hepatic vein performs itself regulating response to the change of intrahepatic circulation receiving neural regulation from these nervous systems, and participates in intrahepatic circulatory regulation cooperating with other intrahepatic vessels. It is assumed natural that there should appear some abnormality in such reflex mechanism, when the function of centripetal fibers conducting informations to the superior center and of centrifugal fibres regulating vasomotoric activity, is disturbed in the regulation mechanism. It is presumed that degeneration of fibers with and without myelin sheath of the hepatic vein in ascitic dogs cause abnormalities in regulative reflex which should be observed in normal dogs, this is also accepted to associate closely to the reports of YOSHITOMI[66] and MORITA[45], in our clinic, concerning the attitude of the sphincter of the hepatic vein at the hepatic artery interruption.

As has been discussed in the above, the nerves of the liver enter not only from the hilum, as has been reported, but from the opening site of the hepatic vein to the inferior vena cava, and the fibers from the latter mainly distribute itself to the system of the hepatic vein. The hepatic vein is controlled by the autonomic and sensory nerve similarly to other intrahepatic vascular systems. Degeneration was observed in the intrahepatic nerves of human cirrhotic liver and that of ascitic dogs resembling liver cirrhosis and there was some correlation between the degeneration and fibrosing process. Such degeneration of the intrahepatic nerves causes the alteration in neural regulation mechanism of the intrahepatic

vascular system. Namely, it is assumed that certain abnormality might be brought about in the function of the hepatic vein which has characteristic sphincter mechanism. This is also interpreted to be a neuropathological demonstration of the findings of MORITA, in our clinic. There was some correlation between morphological change of the nerves of the intrahepatic portal vein and change of portal pressure following the epinephrine administration in ascitic dogs, which well explains the results of epinephrine infusion experiment in cirrhotic liver by CHILD[8], suggesting participation of neurogenic factor in pathologic change of the pressure. The fact that degeneration of intrahepatic nervous element appears in relatively early stage in ascitic dogs, as well as nervous degeneration in human cirrhotic liver, is comprehended to suggest that disturbance of neurogenic factor should not be neglected in the development of cirrhotic liver.

V. SUMMARY

Neuro-histological studies were carried out in the nerve of the liver in normal and ascitic dogs and human cirrhotic liver employing SUZUKI's modification of BIELSCHOWSKY's silver impregnating method and myelin sheath staining of SUGAMO, and change of portal pressure was also studied after epinephrine administration in ascitic dogs. Results obtained are summarized as follows:

1. In the liver of both man and dog, the nerves enter not only from the hilum, as has been reported, but from the opening site of the hepatic vein to the inferior vena cava, fibers from the latter being consisted of the myelinated and unmyelinated fibres as in the hilar area and distributing mainly to the hepatic vein.

2. Both in man and dog, fibres with and without myelin sheath are found to be less compared with those in the hilar area. However, they are abundantly found around the opening site of the hepatic vein to the inferior vena cava.

3. Centripetal fibres of the hepatic vein were abundantly observed in the adventitia of the opening site of the hepatic vein to the inferior vena cava, showing various course, some of which having free endings.

4. Relatively abundant distribution of the fibres was observed around the sphincter of the hepatic vein in dogs. However, it was difficult to find the entrance or distribution of the neural element to the sphincter.

5. Degeneration of the intrahepatic nerves of the hepatic and portal vein and hepatic artery appeared approximately a month after the operation in ascitic dogs, the degree of which advanced as time elasped.

6. Degeneration was observed in the nerve of the hepatic vein and those in the hilar area in human cirrhotic liver, the degree of which being more accentuated than in ascitic dogs.

7. It is presumed that degeneration of the nerves observed in cirrhotic liver of man and dog has close correlation to fibrosing process of the liver.

8. It is assumed that degeneration of the nerves distributing to the hepatic vein in ascitic dogs might cause an abnormality of the hepatic venous function, which neuropathologically demonstrating the report of MORITA[45], in our clinic, that contraction of the hepatic venous sphincter was not observed following hepatic arterial interruption in ascitic dogs different from normal dogs.

9. At portal pressure measurement after epinephrine administration, the pressure gradually arose until a month after the operation in ascitic dogs, which was, however, followed by decrease in the pressure elevation thereafter.

10. Some correlation was observed between change of portal pressure after epinephrine administration and morphological change of the nerves of the intrahepatic portal vein.

Accomplishing the present paper, the author expresses the deepest gratitude to Prof. Dr. ICHIO HONJO for his kind and valuable advices throughout the experiment.

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(* in Japanese)

Figures

Remarks ; "Sugamo's method" is abbreviated to S-method. "Bielschowsky-Suzuki's method" is abbreviated to B-S-method.

Fig. 1. Myelinated bundle(portal vein). ×400 S-method

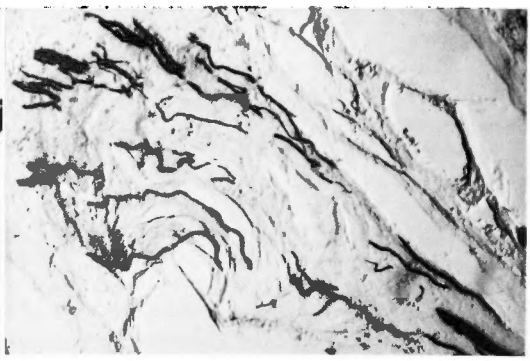

Fig. 2. Myelinated bundle consisted of a number of fibres (hepatic artery). ×150 S-method.

Fig. 3. Myelinated bundle containing extremely large size of fibres (hepatic artery). ×150 S-method

Fig. 4. High power enlargement of Fig. 3, large, moderate and small sizes of myelinated fibres are seen. ×400 S-method

Fig. 5 Bundle bifurcating in a shape of fork, Schwann's cell is seen at the bifurcation (portal vein). ×900 B-S-method

Fig. 6. Bundle bifurcating and communicating in the vessel wall (portal vein). ×650 B-S-method

Fig. 7. Nervous plexus in the wall of bile duct, extremely fine fibres are seen. ×900 B-S-method

Fig. 8. A large bundle becomes gradually fine as it bifurcates, sensory fibres are seen. ×650 B-S-method

Fig. 9. Nervous fibres entering the lobules originating from the nervous bundle in the interlobular artery. ×400 B-S-method

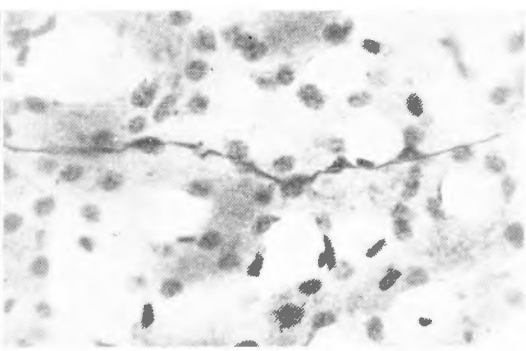

Fig. 10. High power enlargement of Fig. 9, fibres coursing interspace of the hepatic cell cords. ×900 B-S-method

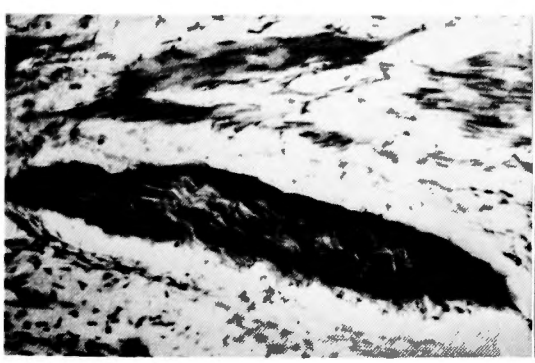

Fig. 11. Nervous bundle entering the liver from the opening site of the hepatic vein to the inferior vena cava along the adventitia of the hepatic vein. ×400 B-S-method

Fig. 12. Nervous bundle in the adventitia of the hepatic vein. ×650 B-S-method

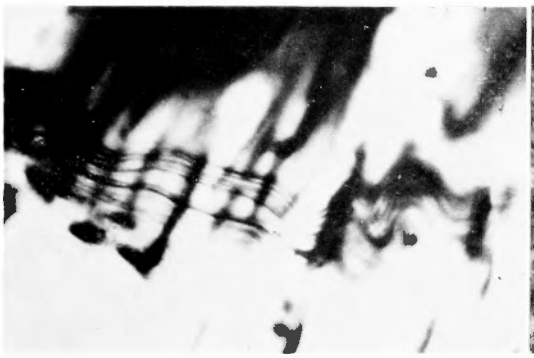

Fig. 13. Unmyelinated bundle in the adventitia of the hepatic vein, fine fibres are abundantly seen. ×650 B-S-method

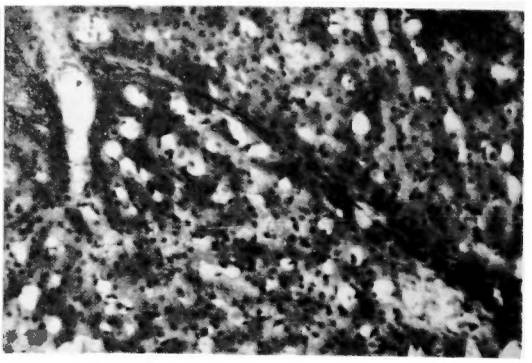

Fig. 14. Nervous fibres along the sublobular vein. ×400 B-S-method

Fig. 15. Myelinated bundle in the adventitia of the hepatic vein. ×150 S-method

Fig. 16. High power enlargement of Fig. 15, fibres of moderate and small sizes are seen. ×400 S-method

Fig. 17. Myelinated bundle in the adventitia of the hepatic vein coursing closely to the media. ×150 S-method

Fig. 18. Myelinated bundle coursing alone (adventitia of hepatic vein). ×400 S-method

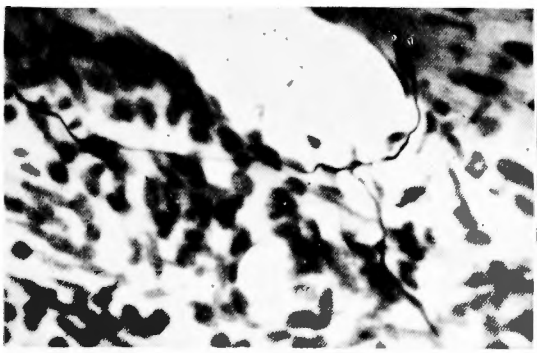

Fig. 19. Centripetal fibres bifurcating in a shape of fork (adventitia of hepatic vein). ×650 B-S-method

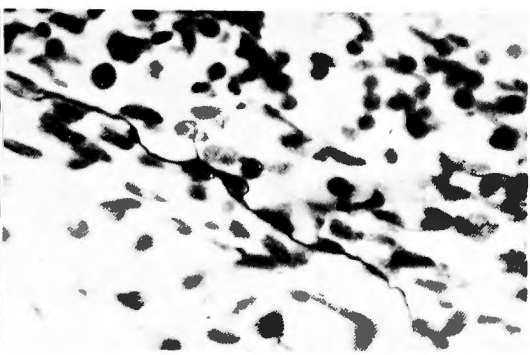

Fig. 20. Centripetal fibres showing loop-like course in parts and providing small branches on the way (adventitia of hepatic vein). ×650 B-S-method

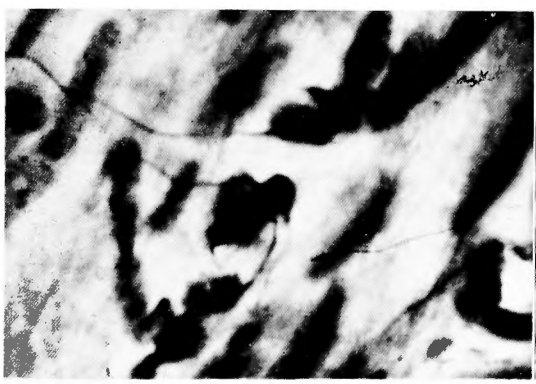

Fig. 21. Centripetal fibres showing spiral winding course after bifurcation (adventitia of hepatic vein). ×650 B-S-method

Fig. 22. Centripetal fibres forming nervous syncytium beside free ending, Schwann's cell is seen aside(adventitia of hepatic vein) ×650 B-S-mehtod

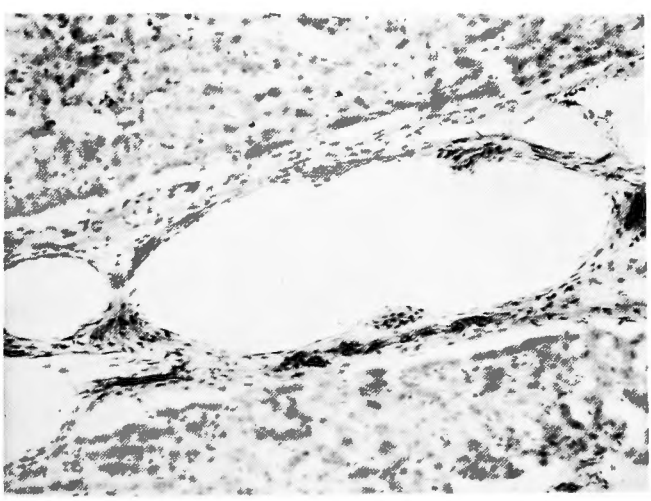

Fig. 23. Autonomic nervous bundle around the sphincter of the hepatic vein. ×150 B-S-method

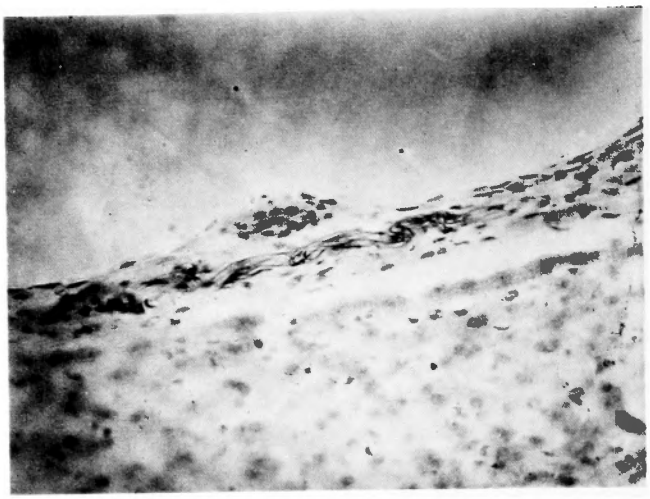

Fig. 24. High power enlargement of Fig. 23. ×400 B-S-method

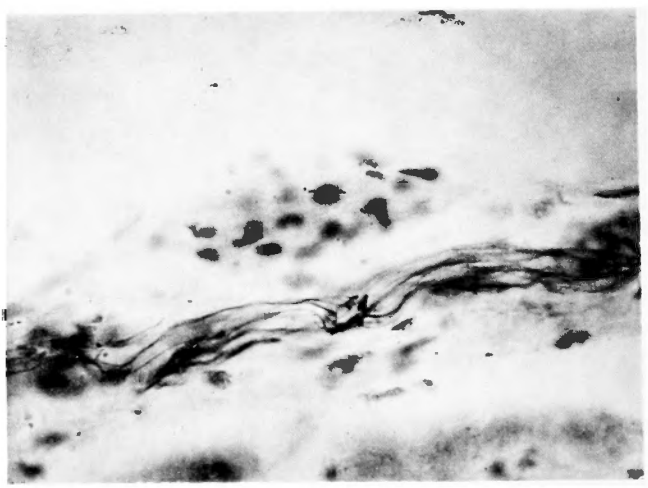

Fig. 25. High power enlargement of Fig. 24. ×650 B-S-method

Fig. 26. Irregular swelling of myelinated fibres (adventitia of hepatic vein in ascitic dog 27 days after operation). ×150 S-method

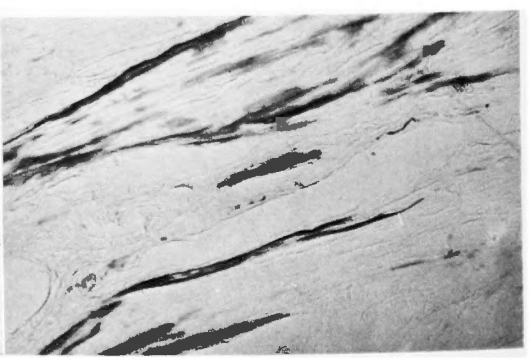

Fig. 27. Drop-like degeneration of myelinated fibres (adventitia of hepatic vein in ascitic dog 27 days after operation). ×150 S-method

Fig. 28. High power enlargement of Fig. 27. ×400 S-method

Fig. 29. Proliferation and swelling of Schwann's cells of the nervous fibers in the adventitia of the hepatic vein(in ascitic dog 27 days after operation). ×400 B-S-method

Fig. 30. High power enlargement of Fig. 29. ×900 B-S-method

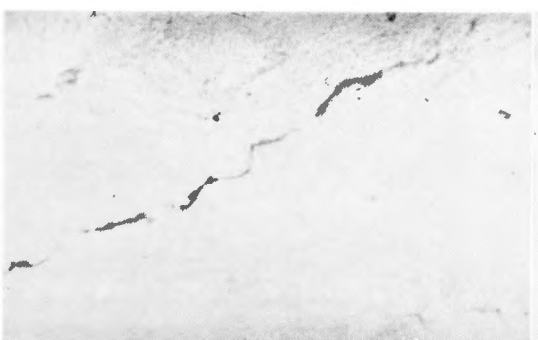

Fig. 31. Irregular swelling and vacuole formation of myelinated fibres (hepatic vein in ascitic dog 36 days after operation). ×200 S-method

Fig. 32. Irregular swelling and vacuole formation of myelinated fibres (portal vein in ascitic dog 36 days after operation). ×400 S-method

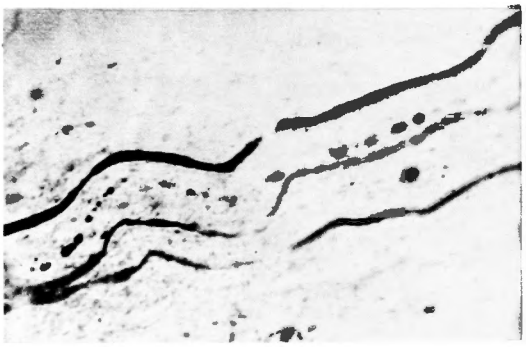

Fig. 33. Drop-like degeneration of myelinated fibres (portal vein in ascitic dog 36 days after operation). ×400 S-method

Fig. 34. Drop-like degeneration of myelinated fibres, irregular degeneration and vacuoles formation can be seen in other fibres (portal vein in ascitic dog 36 days after operation). ×400 S-method

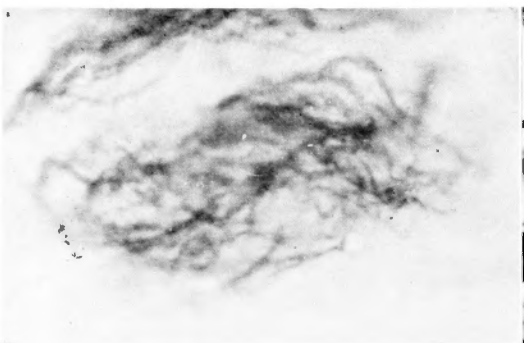

Fig. 35. Bundle showing irregular course of axon (portal vein in ascitic dog 36 days after operation). ×400 B-S-method

Fig. 36. Swelling of Schwann's cells and vacuoles formation in nuclei of Schwann's cells in autonomic bundle of adventitia of the hepatic vein (in ascitic dog 60 days after operation). ×200 B-S-method

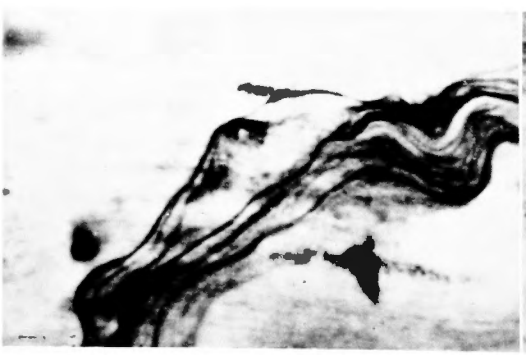

Fig. 37. High power enlargement of Fig. 36. ×900 B-S-method

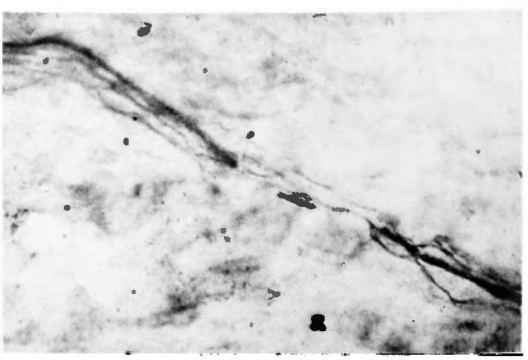

Fig. 38. Autonomic bundle has encountered irregular degeneration and fragmentation, showing fragments of various sizes (hepatic vein of moderate size in ascitic dog 60 days after operation). ×650 B-S-method

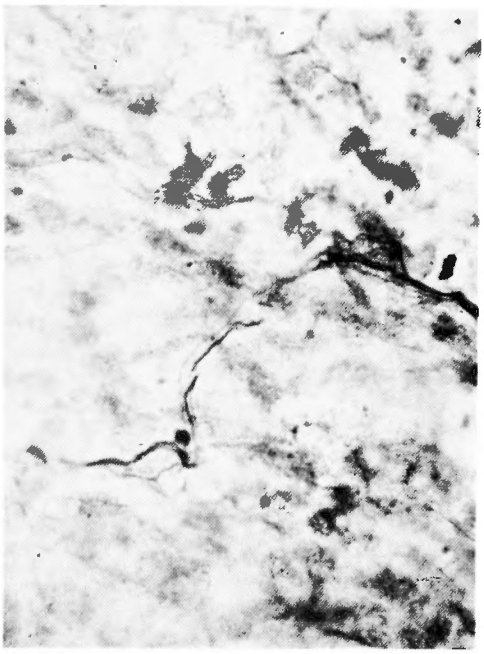

Fig. 39. Withered-tree appearance of nervous fibres, showing fragmentation (hepatic vein of moderate size in ascitic dog 60 days after operation). ×650 B-S-method

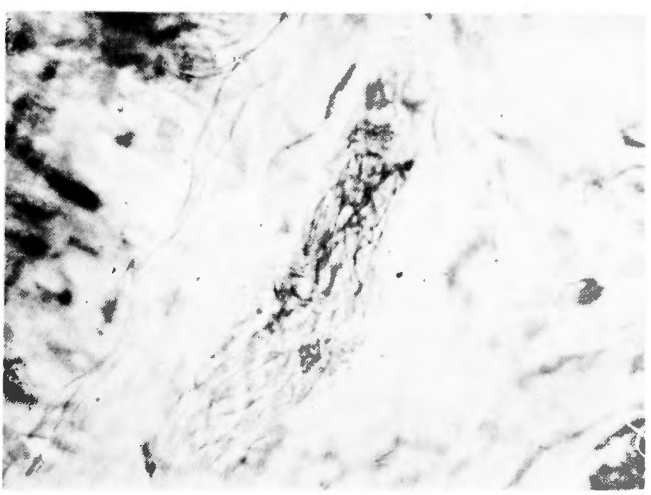

Fig. 40. Irregularly coursing axon, granular degeneration, and fragmentation can be seen in the bundle of autonomic fibres (peripheral portal branches in ascitic dog 60 days after the operation). ×900 B-S-method

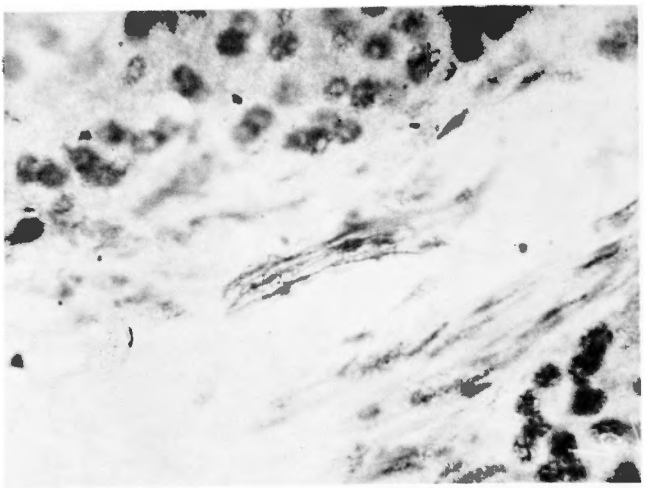

Fig. 41. Granular degeneration of axon in fine bundle of autonomic nerves (peripheral portal branches in ascitic dog 60 days after operation). ×900 B-S-method

Fig. 42. Most of myelinated fibres encountered degeneration and disappearing (hepatic vein in ascitic dog 100 days after operation). ×150 S-method

Fig. 43. Nodular and rosary-like swelling and snake-like winding of myelinated fibres (hepatic vein in ascitic dog 100 days after operation). ×400 S-method

Fig. 44. Severing and disappearing myelinated fibres (hepatic vein in ascitic dog 100 days after operation). ×400 S-method

Fig. 45. Rosary-like degeneration of myelinated fibres (hepatic vein in ascitic dog 100 days after operation). ×400 S-method

Fig. 46. Drop-like degeneration and irregular swelling of myelinated fibres (hepatic artery in ascitic dog 130 days after operation). ×150 S-method

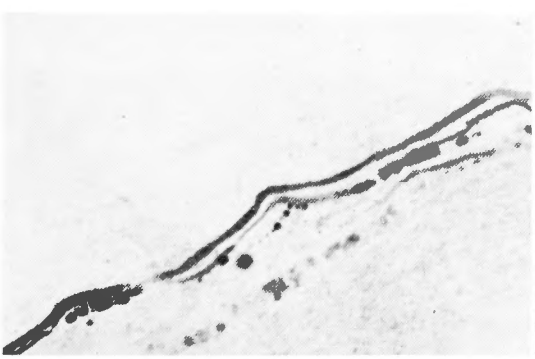

Fig. 47. High power enlargement of Fig. 46. ×400 S-method

Fig. 48. Swelling and fragmentation of myelinated fibres (hepatic artery in ascitic dog 130 days after operation). ×400 S-method

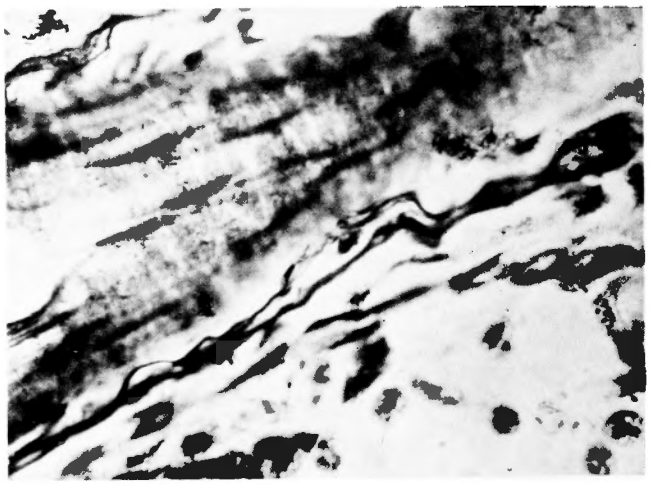

Fig. 49. Fragmentation and vacuole formation of axon in nervous bundle of interlobular artery (in ascitic dog 130 days after operation). ×900 B-S-method

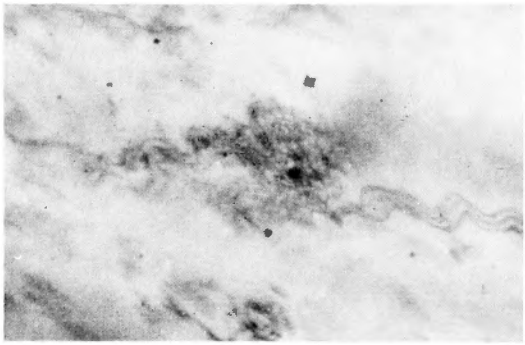

Fig. 50. Irregular course of nervous bundle in interlobular artery (in ascitic dog 130 days after operation). ×900 B-S-method

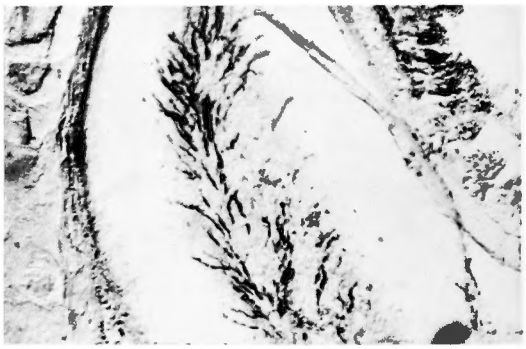

Fig. 51. Degeneration of myelinated fibres along the hepatic artery (hilar area of liver of Laennec's cirrhosis). ×150 S-method

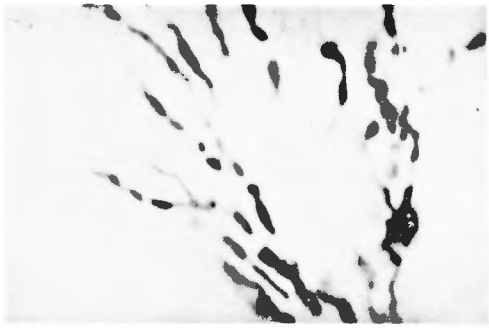

Fig. 52. High power enlargement of Fig. 51. ×400 S-method

Fig. 53. Degeneration of almost entire myelinated fibres, among these bifurcation of myelin sheath can be seen (hilar area of liver of fatty cirrhosis) ×400 S-method

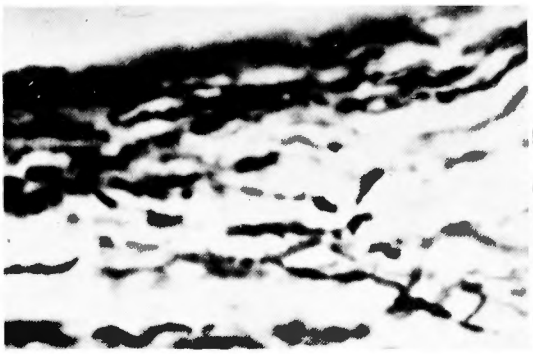

Fig. 54. Degeneration of almost entire myelinated fibres (hilar area -- portal vein of liver of Laennec's cirrhosis) ×400 S-method

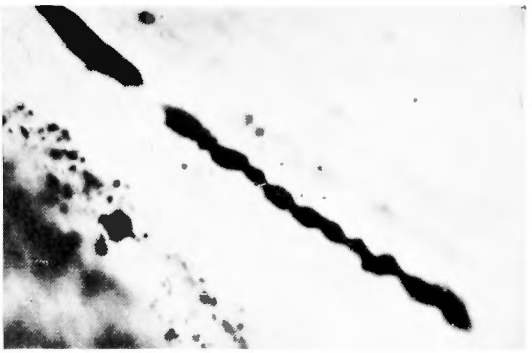

Fig. 55. Rosary-like swelling of myelinated fibres (hilar area of liver of fatty cirrhosis). ×400 S-method

Fig. 56. Nervous bundle along the portal vein (liver of Laennec's cirrhosis). ×150 B-S-method

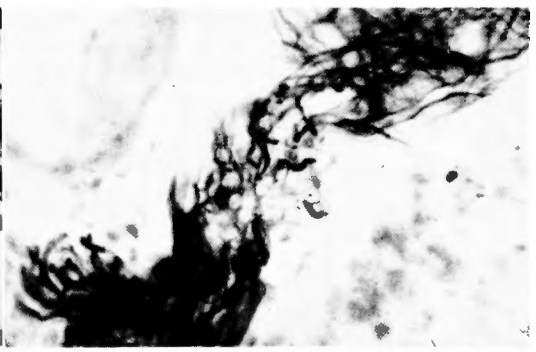

Fig. 57. High power enlargement of Fig. 56, irregular course and fragmentation are seen in axon. ×650 B-S-method

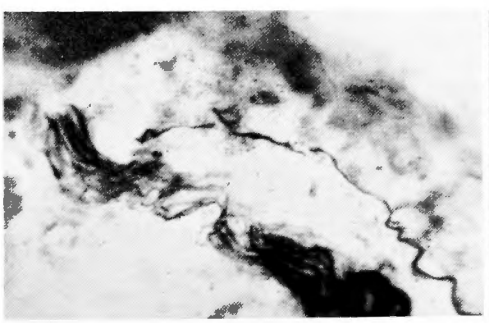

Fig. 58. Fragmentation and winding of autonomic bundle and fragmentation of sensory fibres (hilar area of liver of fatty cirrhosis). ×650 B-S-method

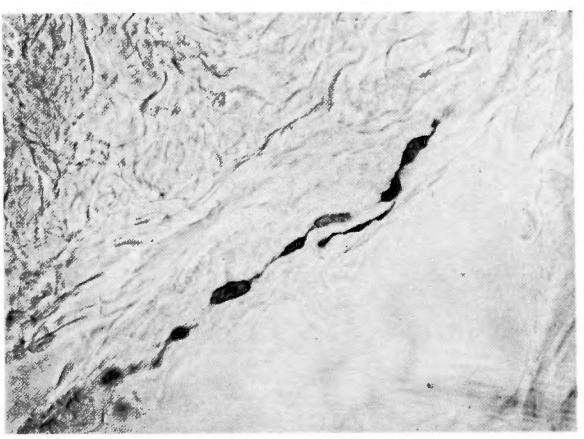

Fig. 59. Swelling of myelinated fibres of the adventitia of the hepatic vein, fragmentation can be seen in parts (liver of fatty cirrhosis). ×400 S-method

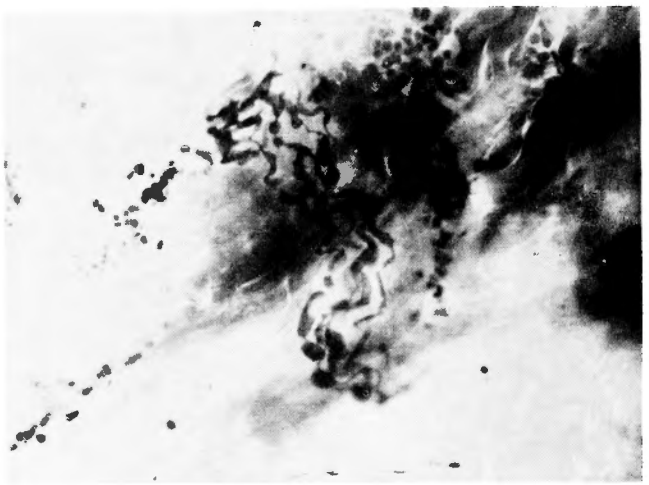

Fig. 60. Degeneration of entire fibres with myelin sheath in the adventitia of the hepatic vein near the opening to the inferior vena cava (liver of Laennec's cirrhosis). ×400 S-method

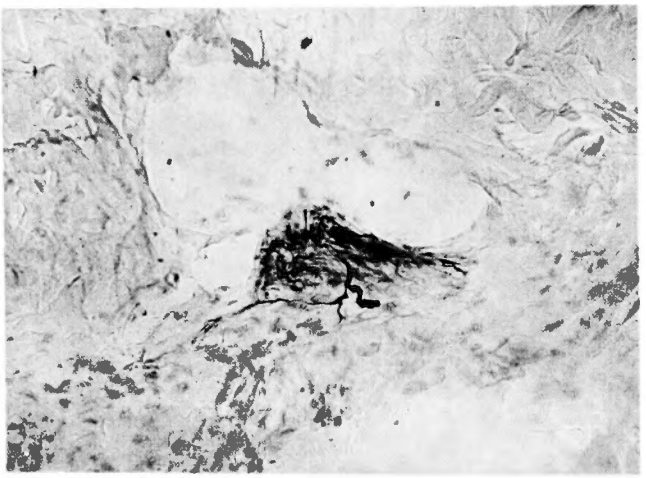

Fig. 61. Irregular swelling, winding and fragmentation of axon and bundle in the adventitia of the hepatic vein (near the opening to the inferior vena cava in liver of Laennec's cirrhosis). ×650 B-S-method

和文抄録

硬変肝の肝内神経について

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長谷部　祐　継

正常犬，腹水犬及び肝硬変症患者の肝臓の神経について，Bielschowsky 氏鍍銀法—鈴木氏変法及び巣鴨氏髄鞘染色法による神経組織学的観察を行ない，また腹水犬におけるEpinephrine投与時の門脈圧の変動を検索し，次の結果を得た．

1）人及び犬において肝臓の神経は従来の報告にある肝門部のみならず肝静脈の下大静脈開口部より肝内に進入し，後者よりの神経線維は肝門部と同様に有髄及び無髄線維よりなり，主として肝静脈系に分布する．

2）人及び犬において肝静脈の有髄及び無髄線維は肝門部の神経線維に比べ少数であるが，下大静脈開口部附近に多く分布する．

3）犬において肝静脈の求心性線維は下大静脈開口部附近の外膜に多く観察され，種々の走行を示し，遊離終末を形成するものも認められた．

4）犬において肝静脈括約筋周囲に可成り豊富な神経分布を認めるが，神経要素の括約筋への進入及び分布は認め得なかつた．

5）腹水犬の肝内神経は術後約1ヵ月より変性を来し，その程度は術後日数の経過とともに進行する傾向を示し，肝静脈，門脈及び肝動脈の神経に変性像を認めた．

6）人の硬変肝において肝門部及び肝静脈に神経変性が認められ，その程度は腹水犬よりも著明である．

7）腹水犬及び人の硬変肝における神経変性はこれらの肝にみられる Fibrosis とその発生過程に於て関連を有するものと考えられる．

8）腹水犬の肝静脈支配神経の変性は肝静脈の機能に異常を来すものと考えられ，このことは腹水犬では正常犬と異り肝動脈遮断後肝静脈括約筋の収縮が認められないと云う教室の森田[45]の報告を神経病理組織学的に実証するものと信ずる．

9）Epinephrine投与時の門脈圧測定において，術後1ヵ月迄の腹水犬では次第に増強する圧上昇を来すが，術後1ヵ月以後の腹水犬では圧上昇の度は低下し，しかも一度上昇した圧は間もなく投与前値を下廻るようになる．

10）腹水犬において，Epinephrine投与時の門脈圧の変動と肝内門脈支配神経の形態学的変化との間に相関性が認められた．